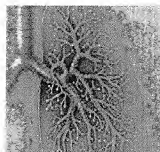


# **EXHIBIT A**

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## INHALED CYCLOSPORINE PRESERVES POSTTRANSPLANT LUNG FUNCTION

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Key Point
Lung transplant patients treated with aerosol cyclosporine may experience long-term preservation of lung function.

**SAN DIEGO**—In lung transplant patients, aerosol cyclosporine may improve long-term preservation of lung function, Aldo Iacono, MD, reported during a presentation at the annual meeting of the American Thoracic Society.<sup>1</sup>

A total of 58 lung transplant recipients were included in the randomized double-blind study. Within six weeks of lung transplantation, and for the following two years, 28 patients received aerosol cyclosporine (300 mg three days a week), while the remaining 30 participants received aerosol placebo. Patients also received systemic immunosuppression and were analyzed by "intent to treat" without loss to follow-up. Findings revealed that FEV<sub>1</sub> decline in patients who were

given aerosol placebo was approximately four times greater than  $FEV_1$  decline in participants who were given cyclosporine. The rates of acute rejection in the aerosol cyclosporine and aerosol placebo groups were 0.44 and 0.46, respectively.

Dr. Iacono said that this study was the first to use inhaled cyclosporine before chronic rejection could develop after lung transplantation.

"Many lung transplant patients develop chronic rejection of the new lung—it is the Achilles heel of the transplant process," said Dr. Iacono, who is Medical Director of Lung Transplantation at the University of Maryland Medical Center and Associate Professor of Medicine at the University of Maryland School of Medicine in Baltimore. "Typically, patients experience a progressive, inexorable decline in lung function, most likely because of this chronic rejection and infections. This finding that aerosolized cyclosporine preserves lung function bolsters our previous findings that the drug reduces chronic rejection of the lung."

Dr. Iacono and colleagues had previously reported that while inhaled cyclosporine did not improve the rate of acute rejection, it did improve survival and extend periods of chronic rejection-free survival on the basis of both histologic and spirometric analysis.<sup>2</sup>

"In the absence of notable differences in rates of acute rejection, a positive result in terms of chronic rejection was unexpected, since previous studies have linked repeated acute rejection events with chronic rejection," Dr. Iacono and colleagues stated of their previous findings. "Histologically, chronic rejection presents in the airways as bronchiolitis obliterans, whereas acute rejection presents as vasculitis. Bronchioles would have higher local concentrations of a drug as a result of direct aerosol delivery, whereas pharmacokinetic studies suggest a much less substantial vascular concentration of the drug. Therefore, it is possible that aerosol cyclosporine has a local airway anti-inflammatory effect that decreases the likelihood of chronic rejection while having a lesser effect on vascular acute rejection."

Dr. Iacono said, "I am hoping that the lung transplant community can work together to organize a multicenter trial." He stated that the FDA requested further studies after being presented with data on cyclosporine's effect on survival and chronic rejection in June 2005. The researchers' previous findings indicated that

additional research would be necessary "to confirm the magnitude and durability of the observed effects in recipients of single-lung and double-lung transplants," they stated.

"If we find promising results from a new, bigger trial, and the drug becomes readily available, it could make a big difference for lung transplant patients," Dr. Iacono said.

—John Merriman

**Reference**

1. Iacono AT, Johnson BA, Corcoran TE, et al. Preservation of lung function with aerosol cyclosporine in a double-blinded placebo-controlled study. Presented at: annual meeting of the American Thoracic Society; May 23, 2006; San Diego, Calif.
2. Iacono AT, Johnson BA, Grgurich WF, et al. A randomized trial of inhaled cyclosporine in lung-transplant recipients. *N Engl J Med*. 2006;354:141-150.

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